



# AN EXTRAORDINARY COMMITMENT TO ENDING ALZHEIMER'S DISEASE

With a transformational gift, the Epstein Family Foundation has challenged the community to join them in partnering with two leading universities to speed the way toward better treatments and a cure for one of the gravest threats to human health worldwide.



Dan and Phyllis Epstein

*"It is just a matter of time before most people will have someone in their families develop dementia or Alzheimer's, yet there are no viable treatments beyond temporary measures to delay the onset. If, together, we can double our initial investment, just imagine the impact that we can have in creating real solutions for this condition."*

— DAN EPSTEIN

Alzheimer's disease is a progressive neurological disorder that affects more than six million Americans. That number is expected to more than double to 13 million by 2060, barring any breakthroughs in treatment. Despite decades of research into its causes and potential therapies, there are still no effective ways to modify or cure the disease.

The Epstein family has touched many lives through their generous support for higher education and the arts, but the inspiration for this gift is especially personal. Dan and Phyllis Epstein are keenly aware of the feeling of helplessness families experience when a loved one is diagnosed with this disease. Dan's twin brother David suffered from the debilitating effects of Alzheimer's for 15 years and passed away in 2021 as a result of the disease.

The gulf between the widespread impact of Alzheimer's disease and the lack of treatment options inspired the Epsteins to launch a new initiative to speed the way toward meaningful therapies: the *Epstein Family Alzheimer's Research Collaboration*. Their transformational gift has sparked the formation of a research powerhouse that unites UC San Diego Alzheimer's experts with their esteemed peers at USC, breathing new life into our decades-long hunt for better options. **Now, they challenge the community to match their financial commitment in an effort to break down any barriers to discovering effective treatments.**

## ACCELERATING HOPE FOR THOSE SUFFERING

The Epsteins intend to bring about real change for current Alzheimer's patients within the next five to 10 years. They have formed an incredibly capable partnership of experts who are equally committed to that goal. Leveraging the strengths of both universities in the field of Alzheimer's research, the gift will help compress the time between study design, patient recruitment and clinical trials in hopes of expediting the discovery of effective treatments and, ultimately, a cure.

At UC San Diego, this collaboration will support high-potential research through the Alzheimer's Disease Cooperative Study (ADCS). Established at UC San Diego in 1991 with federal backing, the ADCS is the nation's largest and longest-running clinical trial effort focused on addressing Alzheimer's disease. It is led by experts in the field and powered by a sophisticated infrastructure for bringing discoveries made in the lab into the clinical setting. When a promising therapeutic option is identified, the ADCS has the personnel in place to expedite the regulatory approval processes and get it to the patients who need it most as quickly and safely as possible.

With the extraordinary infusion of funding made possible by the Epstein Family Alzheimer's Research Collaboration, the ADCS has identified two research initiatives with exceptional potential for achieving significant advancements in Alzheimer's treatment in the near future:

» **Gene therapy**, a transformational approach that has found success in definitively treating several neurological diseases, but has not yet been fully explored in treating Alzheimer's disease. In other words, a potential cure.

» **"Powder for Pennies,"** a rapid evaluation of existing drugs that show potential for relieving the debilitating symptoms of Alzheimer's disease. This project aims to take advantage of already approved compounds to accelerate the timeline for getting new therapies to patients.

Both research areas benefit from the ADCS's expertise in sequential multiple assignment randomized trials, or SMART trials. These innovative trial designs adapt to incorporate early response to treatment, supporting the screening of more drugs more quickly.



*From left: David and Jane Epstein with Phyllis and Dan Epstein*

**The Epstein Family Alzheimer's Research Collaboration will serve as the academic biopharma engine driving these two promising new therapeutic strategies. The Epsteins intend to inspire a matching commitment from others who recognize the incredible impact this work could have on millions of lives in the near future, bringing hope where there is currently despair.**



*"This is an opportunity of a generation. Our vision is to disrupt the current state of Alzheimer's disease treatment development by innovating new therapeutic approaches and SMART clinical trial designs that accelerate progress in collaboration with others."*

– HOWARD FELDMAN

*Dean, Alzheimer's and  
Neurodegenerative  
Disease Research*

*Professor of Neurosciences  
UC San Diego  
School of Medicine*



## UC SAN DIEGO'S LEADERSHIP IN THE FIGHT AGAINST ALZHEIMER'S

UC San Diego has been at the forefront of Alzheimer's disease research from the very beginning. This is where the disease was first identified as an epidemic in the 1970s and is home to the first major federally funded research and clinical trial initiatives for Alzheimer's.

Our researchers collaborate with colleagues around the world to better understand every facet of the disease, including its basic biology, imaging techniques for diagnosing and studying the disease, new therapeutic approaches, clinical trials and epidemiology.

The federal government recognized UC San Diego's leadership in Alzheimer's research by forming the **Alzheimer's Disease Cooperative Study (ADCS)** in 1991. This agreement between UC San Diego and the National Institutes of Health's National Institute on Aging (NIA) was the first major initiative in the nation to support clinical studies that evaluate treatments for both cognitive and behavioral symptoms of Alzheimer's disease.

The ADCS has the translational medicine process down to a science, thanks in part to UC San Diego's world-class facilities and connections with the surrounding biotech industry. The ADCS is part of UC San Diego's larger Alzheimer's disease ecosystem, including the Shiley-Marcos Alzheimer's Disease Research Center, which follows 500 participants, including those with dementia and those without. This significant and diverse cohort is uniquely positioned to support the clinical trial efforts of the Epstein Family Alzheimer's Research Collaboration.

## AN INNOVATIVE APPROACH TO SOLVING THE ALZHEIMER'S PUZZLE

Despite intensive research over the past 40 years, there has not been a breakthrough therapy for Alzheimer's disease. New discoveries will require entirely new ways of thinking about the problem.

We believe UC San Diego's nontraditional ethos is central to unlocking the mysteries of Alzheimer's disease. We aim to rethink the established paths toward new therapeutics and reveal novel ways to intervene in the relentless progression of Alzheimer's disease.

Two hallmarks of UC San Diego that make it an exceptional place for addressing this baffling disease include:

- » Its proclivity for taking an unconventional approach to complex endeavors, working across disciplines to break down barriers and find new and creative ways to solve problems.
- » Its successful and well-established track record for translational medicine. Our state-of-the-art facilities and exceptional pool of talent allow us to speed new ideas through the required drug development pipeline.

### Through their vision and generosity, the Epstein family is jump-starting a new era in

**UC San Diego's quest for effective treatments for Alzheimer's disease.** They are enabling us to intensify our focus on the most promising paths toward a cure. With their infusion of funding – along with matching gifts – we aim to fully leverage UC San Diego's unconventional spirit of innovation to speed the way toward meaningful, long-awaited advancements in Alzheimer's treatment.

## MILESTONES IN ALZHEIMER'S RESEARCH AT UC SAN DIEGO

1976

Robert Katzman, MD, founding director of the Shiley-Marcos Alzheimer's Disease Research Center at UC San Diego, is the first person to declare Alzheimer's disease a "major killer" in an article in the Archives of Neurology journal.

1991

Leon Thal, MD, establishes the Alzheimer's Disease Cooperative Study at UC San Diego in partnership with the National Institutes of Health. It is the first nationwide effort to test new Alzheimer's drugs and investigate new methods for conducting dementia research.

2001

The first-in-human clinical trial of gene therapy in an adult brain to treat Alzheimer's disease is conducted by Mark Tuszynski, MD, PhD, director of the UC San Diego Translational Neuroscience Institute.

2012

The first stem cell-derived in vitro models of Alzheimer's disease from patients with the illness are created by Larry Goldstein, PhD, UC San Diego professor of cellular and molecular medicine.



*"It has required decades of focused work to get to this point, but we've found in animal studies that delivering BDNF to the parts of the brain that are affected earliest in Alzheimer's disease results in reversal of loss of neuronal connections and protects against ongoing cell loss. Gene therapy isn't new, but its potential in treating Alzheimer's disease in people is largely untapped."*

– MARK TUSZYNSKI, MD, PHD

*Distinguished Professor of  
Neuroscience*

*Director, Translational  
Neuroscience Institute  
UC San Diego School of Medicine*



## GENE THERAPY FOR ALZHEIMER'S DISEASE: A HIGH-RISK, HIGH-REWARD APPROACH

An emerging treatment called gene therapy enables us to modify genes to correct defects that occur in inherited forms of disease, essentially stopping the progression of the disease in its tracks.

In fact, it has cured a neurological condition called spinal muscular atrophy, which affects children at birth. Its application in Alzheimer's disease is untapped, holding the promise of conclusively addressing the genetic mutations that cause familial inherited forms of this disease. It is an entirely different approach to current treatments, which are based on remediating the pathologies of the disease, including amyloid plaques and tau neurofibrillary tangles, and have not yet achieved clinical success.

This approach is particularly compelling and is a focus of the Epstein Family Alzheimer's Research Collaboration because of its profound potential implications. It is now possible to edit genomes to alter DNA sequences and modify gene function. **If we are able to modify specific mutations that lead to Alzheimer's disease, gene therapy could be the cure.**

This effort will build on UC San Diego's existing leadership in Alzheimer's disease gene therapy treatment. For more than two decades, Mark Tuszynski, MD, PhD, distinguished professor of neuroscience and director of the Translational Neuroscience Institute at UC San Diego School of Medicine, and his colleagues have advanced foundational studies that laid the groundwork for this approach. He led a phase I clinical trial that assessed the safety and effects of injecting nerve growth factor into the brains of patients diagnosed with Alzheimer's disease to slow or reverse neuronal degeneration.



That work led to the announcement last year of a new, first-in-human clinical trial to assess the safety and efficacy of delivering a specific protein called brain-derived neurotrophic factor (BDNF) into the brains of patients with Alzheimer's disease or mild cognitive impairment. BDNF is part of a family of growth factors found in the brain and central nervous system that support the survival of existing neurons and promote growth and differentiation of new neurons and synapses. BDNF is particularly important in regions of the brain susceptible to Alzheimer's disease degeneration.

The Epstein's gift will also leverage the efforts of Subhojit Roy, MD, PhD, professor of neuroscience and pathology. Roy's laboratory is developing a new Alzheimer's gene therapy using CRISPR technology, targeting key genes that are involved early in the disease. His team will work with colleagues at USC who have identified and followed families with a specific gene mutation found in the Jalisco region in Mexico that predisposes them to early-onset Alzheimer's disease, often appearing in their 30s and 40s.

While these efforts to advance gene therapy are exciting on their own, they become vastly more impactful when paired with the Alzheimer's Disease Cooperative Study (ADCS)'s strengths in translational medicine. The ADCS is adept at taking new therapies through early clinical trials using innovative designs to more quickly identify the most significant findings.





*“Repurposed medicines don’t have the same degree of intellectual property protection, and they can be made available at a much cheaper price to the public. We really need something like that for Alzheimer’s disease, which has such a high prevalence in older people.”*

– **HOWARD FELDMAN**

*Dean, Alzheimer’s and  
Neurodegenerative  
Disease Research*

*Professor of Neurosciences  
UC San Diego  
School of Medicine*



## POWDER FOR PENNIES: LEVERAGING WHAT WE ALREADY KNOW

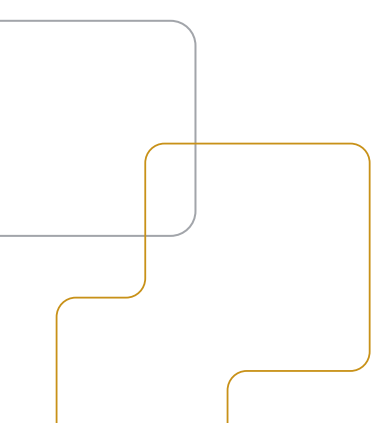
Significant time and funding are required to prove the safety and efficacy of a new drug, but what about existing drugs that are approved for use but whose full capabilities are not yet known?

Instead of investing millions into the development of one drug, the Powder for Pennies (P4P) program aims to power through hundreds of existing therapies to identify those that show promise for treating Alzheimer’s disease.

A recent example being considered is bumetanide, an oral diuretic or “water pill” approved for treating congestive heart failure, which looks to have a potentially potent effect in Alzheimer’s disease and offers a path to early clinical trials.

P4P leverages the ADCS’s network of labs and collaborators and its deep expertise in conducting early phase clinical trials of candidate treatments. Once compounds of promise are identified and have been through their early stages of testing, they can be handed off to USC’s Alzheimer’s Therapeutic Research Institute for phase III trials or larger-scale investigation. The program involves collaborators at USC, Harvard University and other research centers across the country.

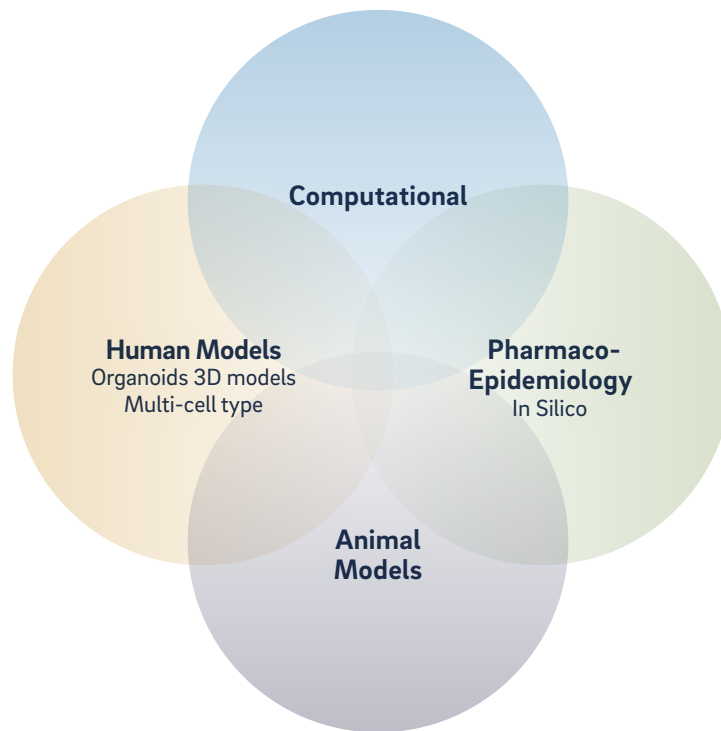
P4P takes advantage of our existing, powerful translational medicine infrastructure, including the diverse participant cohorts at the Shiley-Marcos Alzheimer’s Disease Research Center and the clinical trials engine of the Alzheimer’s Disease Cooperative Study. By employing adaptive trial designs, the ADCS is able to tailor interventions to an individual’s response and adjust the therapies to explore other promising options.



Adaptive trials enable us to more quickly cycle through successful and unsuccessful therapeutic candidates instead of focusing each trial on one treatment path. It eliminates the engrained mindset to “make it work” due to long investments in the drug itself, instead supporting our ability to accelerate decision making based on the efficacy of the potential treatments.

These innovative trials represent just one of the ways the ADCS can evaluate and refine new treatments. Thanks to funding through this new collaboration, we can also simultaneously analyze new therapeutic candidates through animal models, computational analysis, pharmacology-epidemiology assessments, human brain organoids and more, as depicted in the “propeller model” below. Together, these approaches create a richer and more accurate picture of potential candidates for Alzheimer’s treatments that may otherwise be overlooked.

### PROPELLER MODEL FOR EVALUATING EXISTING THERAPIES







*"If you want to do something transformational, you need a lot of key ingredients. It's not just a matter of throwing dollars at it. There needs to be an overall recognition and understanding of the problem, a plan for involving others in coming up with solutions, and an approach that will engage others in the community to support it so you can make some real advancements.*

*When you have the opportunity to support something in a meaningful way, you take a look at the community, take a look at the needs, and at the end of the day you have a sense that you made a difference. That's what we've tried to do through our family and our foundation — to make a difference."*

— DAN EPSTEIN



## ONE PLUS ONE EQUALS THREE

Collectively, we must make breakthroughs that could relieve the burden Alzheimer's disease brings to our health care systems, our economy, and the well-being and productivity of those it impacts. Yet despite the progress we have made to better understand this disease, there are no adequate therapies to fight against it.

The need to find safe and effective treatments for Alzheimer's disease that are accessible to diverse communities is paramount, and the time to pursue new therapeutic options is now. The Epstein Family Alzheimer's Research Collaboration is a commitment to the high-risk, high-reward pursuit of a potential cure that gene therapy offers, as well as a concerted effort to fast-track existing medications that could be widely available, affordable and practical.

Our goal is to offer hope in situations where there is currently none. Today, there is no way to slow the progression of Alzheimer's disease, let alone to halt it or reverse symptoms. If we can make advancements in any of these areas, we will have made a difference.

Within five years, we intend to identify five to 10 compounds for treating this disease that we can deliver directly to the people who need them. The steps we need to turn this dream into reality can only occur with academic rigor among leading universities such as UC San Diego and USC. Philanthropic investment is the catalyst that can accelerate early-stage research so these goals can be achieved.

Beyond the Epstein's initial \$50 million investment to establish the Epstein Family Alzheimer's Research Collaboration, the couple has challenged USC and UC San Diego to raise an additional \$25 million each to support Alzheimer's research.



If you would like to join the Epsteins in their ambitious, potentially historic contribution to science and human health, we invite you to contact Whitney Egan at [wnegan@ucsd.edu](mailto:wnegan@ucsd.edu) or (858) 246-1561 to learn more, or visit [giving.ucsd.edu/epstein-challenge](https://giving.ucsd.edu/epstein-challenge) to give today.

**THANK YOU** for considering making a gift to support the Epstein Family Alzheimer's Research Collaboration and partnering with us to realize a future of promise for those impacted by Alzheimer's.

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*"Our intention is to leverage this foundational funding and to double, triple or quadruple it through grants that arise from the data we will generate from their gift. This is the accelerator step. Government funding agencies will support a project once it has generated some proof, not when it's an idea. This seminal money helps us move ideas from the labs to the clinic, where they can begin to be tested more readily. Philanthropy holds the extraordinary potential to make that happen."*

**– HOWARD FELDMAN**

*Dean, Alzheimer's and Neurodegenerative Disease Research  
Professor of Neurosciences, UC San Diego School of Medicine*

